Chronic diarrhoea-all in the bowel?

S Gupta[1] C J Tibbs[2] M J G Farthing[3]
R C G Pollok[4]

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Chronic diarrhoea is a common presenting symptom of patients attending gastroenterology clinics. When routine tests fail to reveal a cause for the diarrhoea, rarer causes need to be excluded. We report such a case where a diagnosis of medullary thyroid carcinoma (MTC) was eventually made. The patient underwent radical surgery with amelioration of her symptom. Diarrhoea is rarely the presenting symptom of MTC but it should be considered in the differential diagnosis of chronic diarrhoea. Measurement of serum calcitonin should be included in the investigation of difficult chronic diarrhoea.

CASE REPORT

A 44-year-old woman was referred with an 18-month history of chronic diarrhoea. This had started soon after her husband had sustained traumatic brain injury and was admitted for neuro-rehabilitation. The symptoms appeared to be worse during periods of stress. At initial assessment she had a bowel frequency of 12 motions/day and watery stools without blood. There were no other associated symptoms. She took no regular medications and denied laxative use. She had tried cholestyramine, reflexology and homeopathy without benefit, and was on loperamide as required with limited benefit. She was an office worker. There was no family history of diarrhoea or other endocrine problems. She consumed no alcohol and smoked 10 cigarettes a day. Initial clinical examination was normal.

A 3-day out-patient stool collection for weight was elevated, with an average stool weight of 620 g/day (normally 200 g/day), suggesting an organic cause to her diarrhoea. Further investigations were normal, including serum vitamin B_{12}, red cell folate, thyroid function test, serum IgA anti-endomysial antibodies, serum immunoglobulins, 24-h urinary catecholamines and 5-hydroxy-indole acetic acid (5HIAA), and gut hormone profile (gastrin, vasoactive intestinal polypeptide, somatostatin, glucagon, pancreatic polypeptide and neurotensin). A urinary laxative screen by thin layer chromatography was negative. Biopsies of distal duodenum, terminal ileum and colon obtained at upper gastrointestinal endoscopy and ileo-colonoscopy were normal. Ultrasound and CT scan of the abdomen and pelvis

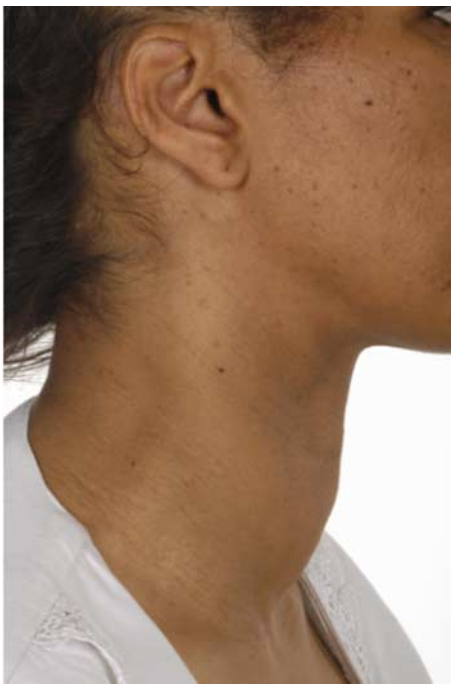

Figure 1 **Showing thyroid gland enlargement and cervical lymph node enlargement.** [In colour online.]

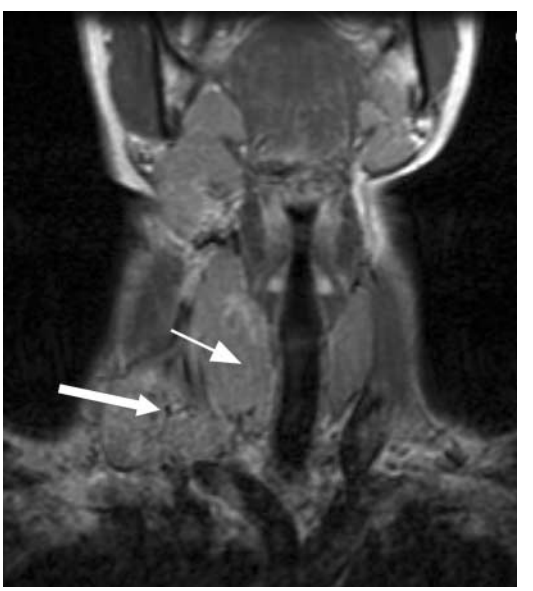

Figure 2 **MRI T2 weighted images of neck coronal view showing enlargement of right lobe of thyroid gland (thin arrow) and right side cervical lymphadenopathy (thick arrow).**

[1]Locum Consultant Gastroenterologist, Mayday University Hospital, Croydon, Surrey, UK; [2]Consultant Gastroenterologist, Royal Surrey County Hospital, Guildford, Surrey, UK; [3]Consultant Gastroenterologist and Principal, and [4]Consultant Gastroenterologist and Honorary Senior Lecturer, St George's Hospital and Medical School, London, UK

Correspondence to: Dr Sanjay Gupta

E mail: sanjay.gupta@mayday.nhs.uk

showed no abnormality. Analysis of stool for fat globules was negative.

The patient was subsequently noted to have diffusely enlarged thyroid gland (Figure 1). An ultrasound scan of the neck showed a $3 \times 3 \times 5$ cm heterogeneous hypoechoic mass lesion in the right lobe of the thyroid, with multiple local nodes displaying a similar echo texture and with marked hypervascularity displaying a chaotic pattern. A fine needle aspiration from the thyroid mass and the local lymph nodes was diagnostic of MTC, as well as parenchymal infiltration by spindle and oval shaped cells with occasional cytoplasmic granularity positive for chromogranin A, carcinoembryonic antigen and glycoprotein P. Further imaging by CT and MRI (Figure 2) were indicative of local and pulmonary metastatic disease. The serum calcitonin was markedly elevated at 19,315 ng/L (normal 0–11.1 ng/L). The patient underwent a total thyroidectomy, right selective neck dissection and thymectomy, resulting in a reduction of serum calcitonin to 885 ng/L and complete resolution of her diarrhoea. Histology of the resected specimen confirmed the diagnosis of MTC with lymphovascular invasion, extracapsular spread and metastasis to the lymph nodes. Postoperatively, a radio-labelled octreotide scan showed no local or pulmonary uptake. She was given postoperative intensely modulated radiotherapy and commenced on thyroxine. Family screening was recommended.

DISCUSSION

MTC comprises 3–10% of thyroid gland malignancies. Its origin from the parafollicular C cells puts it in the category of neuroendocrine tumours. It can occur as a sporadic type (84%) or hereditary familial type (16%) in association with autosomal dominant multiple endocrine neoplasia (MEN) Type 2 syndrome.[1] The familial group is associated with the abnormalities of the *RET* proto-oncogene and this also occurs in 4–10% of sporadic cases.[2] Following genetic counselling, *RET* analysis of this patient was found to be normal.

Presentation of MTC with chronic diarrhoea is very unusual.[3,4] The most common presentation of MTC is a painless lump in the thyroid. Less commonly, the patient may present with pain, dysphagia or hoarseness. It may also be found on screening for MTC as a part of MEN syndrome or a family member of a patient with MEN. At initial presentation, the thyroid swelling may be associated with cervical lymphadenopathy in up to of 75% cases; the swelling may not always be palpable.[5] Following initial diagnosis of MTC, up to 30% of patients may develop diarrhoea; it is a poor prognostic marker associated with bulky disease, high calcitonin levels or metastatic disease.[6–8] The standard thyroid function tests are normal, differentiating MTC from the epithelial tumours of the thyroid gland.

Investigations for diagnosing MTC include ultrasonography of the thyroid and regional lymph nodes followed by fine needle aspiration biopsy. Computed tomography scan can be done for the primary tumour and metastases. Elevated concentrations of serum calcitonin are used as a biochemical marker for screening, diagnosis and follow up of disease. Basal and 'pentagastrin' stimulated calcitonin assays are done in patients suspected to have MTC. In our patient, hormonal assay of catecholamines and 5 HIAA were normal, as was *RET* analysis, thus excluding pheochromocytoma (which can be bilateral in MEN 2A or 2B in 40–50% of cases[9]) and carcinoid syndrome, both of which are associated with MEN type 2A or 2B. Ultrasound scan and computed tomography of the abdomen and pelvis showed no evidence of metastasis, although computed tomography of the chest showed pulmonary metastasis. Histology of the thyroid gland can show diffuse or nodal patterns of involvement. Immunohistochemical staining shows that MTC contains calcitonin,

Table 1 **Causes of chronic diarrhoea[25]**

Colonic	Colonic neoplasia
	Ulcerative colitis and Crohn's colitis
	Microscopic colitis
Small bowel	Coeliac disease
	Crohn's disease
	Other small bowel enteropathies (e.g. Whipple's disease, tropical sprue, amyloid, intestinal lymphgiectasia)
	Bile acid malabsorption
	Disaccharidase deficiency
	Small bowel bacterial overgrowth
	Mesenteric Ischaemia
	Radiation enteritis
	Lymphoma
	Giardiasis (and other chronic infection)
Pancreatic	Chronic pancreatitis
	Pancreatic carcinoma
	Cystic fibrosis
Endocrine	Hyperthyroidism
	Diabetes
	Hypoparathyroidism
	Addison's disease
	Hormone secreting tumours (VIPoma, gastrinoma, carcinoid)
Other	Factitious diarrhoea
	'Surgical causes' (e.g. small bowel resections, internal fistulae)
	Drugs
	Alcohol
	Autoimmune neuropathy

carcinoembryonic antigen, chromogranin A and neuron specific enolase.[10–12]

The mechanism of diarrhoea is not well characterized. Complete removal of the tumour results in resolution of diarrhoea but it persists if metastasis is present, suggesting that it is mediated hormonally.[13] Watery diarrhoea with or without steatorrhoea may occur either before the diagnosis of the primary tumour or during the course of the metastatic disease.[14] Calcitonin-induced secretory diarrhoea may be an important mechanism[15] that may be independent of cyclic adenosine monophosphate.[16] Other potential mediators of diarrhoea include prostaglandins,[17] calcitonin gene-related peptide,[18] serotonin,[19] histaminase,[20] kallikrein[17] and dopa-decarboxylase.[21] The diarrhoea may be related to disordered intestinal motility,[19] but secretory mechanisms are clearly important.[22] Elevated levels of prostaglandin E2 and F2 α have been detected in plasma and tumour material from some patients,[17] which may cause secretion of salt and water, especially in the ileum.[23] However, prostaglandins have not been consistently elevated in patients with MTC and diarrhoea.[17] Calcitonin infused into normal subjects has been shown to induce a net intestinal secretion in the jejunum.[24]

Measurement of daily stool weight is a simple and inexpensive way to identify patients with an organic cause for their diarrhoea. The causes of chronic diarrhoea are shown in Table 1.[25] MTC is a rare but important non-gastrointestinal cause of diarrhoea. It should be suspected in patients in whom gastrointestinal causes of chronic diarrhoea have been excluded, especially if a thyroid mass is palpable. We support the notion that the measurement of serum calcitonin be added to the investigations recommended to investigate patients with unexplained difficult chronic diarrhoea.[25]

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